and B submitted herewith. Appendix A is a marked-up copy of the amendments to the specification and Appendix B is a clean copy of the amendments to the specification.

After the Abstract, please insert the Sequence Listing attached hereto as Appendix E.

IN THE CLAIMS

Please amend the claims as indicated in Appendices C and D submitted herewith. Appendix C is a marked-up copy of the amended claim and Appendix D is a clean copy of the amended claim.

REMARKS

Claims 1-12 and 14-15 are presently pending in the captioned application. In response to the objection under 37 C.F.R. §§1.821-5 for sequence listings, applicants supply herewith a computer readable copy and amended specification containing the requested sequence listing for the amino acid sequence at page 3, line 3. Applicants respectfully submit that sequence listings for the remaining amino acid sequences disclosed in the instant application are not required under 37 CFR § 1.821(a)(2) since they each contain a D-amino acid. Additionally, all remaining objections to the specification regarding margins, spelling and punctuation are similarly addressed herewith.

The amendments are presented in the expectation that the amendments will place this application in condition for allowance.

The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of claims 1-12, 14, and 15 under 35 U.S.C. § 103

The Office Action states that claims 1-12, 14, and 15 are rejected under 35 U.S.C. § 103 as being obvious. The Office Action rejects claims 1, 2, 5-12, and 14 over Nath et al. (Novel Met-Enkephalin Analogue, Pharm. Res. Vol. 31, No. 5, pages 269-273 (1995)) in view of Chiesi et al. (U.S. Patent No. 5,855,916); claims 1-3 and 7-11 over European Patent Application No. 0 463 653 ("'653") in view of Nath et al.; claims 1, 2, 4, 7-12, and 14 over Hora et al. (U.S. Patent No. 5,977,856) in view of Nath et al.; and claims 1, 7-12, and 15 over French Patent 2 710 268 ("'268") in view of Nath et al.

Applicants respectfully traverse this rejection because all three prongs for a *prima facie* case of obviousness have not been established for each of the rejections. Specifically, all the claim limitations are not present in the cited references and one of ordinary skill in the art would have no motivation to modify the cited references into the present invention.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and

(3) that the prior art references teach or suggest all the claim limitations. In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

1. Rejection of claims 1, 2, 5-12 and 14 over Nath et al. in view of Chiesi et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, 5-12, and 14 are rejected under 103 U.S.C. 103(a) as being obvious over the Nath et al article in view of Chiesi et al. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . .the Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative. Chiesi et al teach forming an inclusion complex of a basic drug and a cyclodextrin such as hydroxypropyl-β-cyclodextrin and dimethyl-β-cyclodextrin. The inclusion complex results in improved storage stability and enhanced water solubility and enhanced water solubility and bioavailabilty for the drug. The drug is to be administered orally or parenterally...It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide of the Nath et al. article

with the cyclodextrins of Chiesi et al in order to form inclusion complexes for pharmaceutical administration because the opioid peptide of the Nath et al. article is a basic drug as required by Chiesi et al and because combining the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al would have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and cyclodextrin derivative in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

The presently claimed invention relates to inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the essential components. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. This compound is not the same as the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide used in accordance with the presently claimed invention. The Nath et al.

compound is different from the compound used according to the presently pending claims in that it contains a MePhe group, rather than a N-MePhe group. Additionally, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

Chiesi et al. do not remedy these deficiencies. Chiesi et al. disclose multicomponent inclusion complexes containing a basic-type drug, a cyclodextrin, and an acid as the essential components. The presence of acid in these inclusion complexes results in water soluble complexes. Chiesi et al. provide no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the basic-type drugs used in the disclosed inclusion complexes. Additionally, Chiesi et al. provide no teaching for inclusion complexes that do not contain an acid as an essential component.

Applicants claims as presently amended are limited to inclusion complexes containing an opioid peptide and a cyclodextrin derivative as the only essential components. Neither reference cited by the Examiner teaches inclusion complexes having only these two essential components. As shown above, Nath et al. merely teaches a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, Chiesi et al. teach inclusion

complexes which require a basic-type drug, a cyclodextrin derivative, and an acid. The acid is a critical component of the inclusion complexes taught by Chiesi et al. In contrast, the presently claimed inclusion complexes do not contain an acid. Accordingly, the presently claimed invention is patentably distinct from the references cited by the Examiner.

Additionally, a person of ordinary skill in the art would recognize that the opioid peptide used according to the presently claimed invention is already soluble in water and stable. Accordingly, this peptide does not require improved water solubility or stability. Instead, the presently claimed inclusion complexes provide excellent analgesic effects without any side effects for oral administration. Neither reference cited by the Examiner disclosed inclusion complexes containing an opioid peptide and a cyclodextrin which can be administered orally. Indeed, as evidenced by Uekema et al., *Drug Targeting Delivery*, 1994, 3, 411-456, there is a great deal of uncertainty when it comes to actual formation of complexes with opioid peptides and cyclodextrins. Accordingly, a person of ordinary skill in the art would have had no reasonable expectation of success in forming orally available inclusion complexes containing the specific peptide according to the presently claimed invention as well as a cyclodextrin as required by Amgen, Inc. v. Chugai Pharm. Co. without an express teaching to do so from the references cited by the Examiner.

In particular, applicants have observed that the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide combined with beta-cyclodextrin in a 1:2 ratio is more effective orally than a 1:1 ratio. In the case of transdermal delivery, the effectiveness of these complexes is reversed. This shows that the formation of the presently claimed inclusion complexes containing this specific opioid peptide and a cyclodextrin would not have been obvious to a person of ordinary skill in the art without an express teaching to do so. Neither reference cited by the Examiner contains such an express teaching. Accordingly, the references cited by the Examiner merely provide an invitation to experiment. These references do not predict that any drug can be combined with cyclodextrins to form orally effective pharmaceutical compositions, nor do they teach how opioid peptides will behave when combined with cyclodextrins.

Accordingly, a person of ordinary skill in the art would have had no motivation to combine these references to arrive at the presently claimed invention without impermissible hindsight. See In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999). The presently claimed complexes were not achieved or suggested by the prior art given that the varying parameters and innumerable possibilities that would have had to be tried until the successful combination was arrived at. Since the prior art does not indicate which parameters are critical, or how the opioid can be expected to

behave with cyclodextrin, the only direction as to which if the many choices is likely to be successful is impermissibly provided by the present application. "When a rejection depends on a combination of prior art references there must be some teaching, suggestion, or motivation to combine these references." In re Rouffet, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). As stated herein, no such motivation is present in the cited references.

Furthermore, one of ordinary skill in the art would not have been motivated to make the claimed invention based on a reference teaching water solubility where improved water solubility is not an object of the invention. The peptide included in the presently claimed invention is already soluble in water; accordingly, there is no need to improve its water solubility or stability by including an acid, as required by Chiesi et al. A person of ordinary skill in the art attempting to make orally available inclusion complexes having improved analgesic properties, as required by the presently claimed invention, would have had no motivation to combine the teachings of Nath et al. with the Chiesi et al. reference related to a completely unrelated art area, i.e. preparation of complexes having improved solubility. Accordingly, the combination cited by the Examiner does not render the presently claimed invention obvious.

Additionally, there has been a long felt need for an innovative strategy for oral delivery of peptide based drugs. As

shown by Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986), long felt need is a secondary consideration which may be used as an indicia of non-obviousness. To satisfy this need, applicants have developed pharmaceutical compositions comprising this specific peptide with a cyclodextrin to impart improved analgesic activity with longer duration of action as compared to free peptides (see page 6 of the instant specification). Applicants claimed invention is not a mere combination, but a composition having improved oral efficacy. This is not taught by the cited references, as required by In re Wilson.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Chiesi et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 5-12, and 14.

2. Rejection of claims 1-3 and 7-11 over EP '653 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1-3 and 7-11 are rejected under 103 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalins, with cyclodextrins, especially B-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. . . . The European Patent Application '653 does not teach

> administration of Applicant's particular opioid peptide. The Nath et al. article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the European Patent Application '653 because the opioid peptide of the Nath et al article is a specific known example of the peptide and enkephalin drugs which are contemplated by the European Patent Application '653 and because administering the opioid peptide of Nath et al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to inclusion complexes comprising an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a

cyclodextrin derivative. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. This compound is not the same as the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide used in accordance with the presently claimed invention. The Nath et al. compound is different from the compound used according to the presently pending claims in that it contains a MePhe group, rather than a N-MePhe group. Additionally, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

EP '653 does not remedy these deficiencies. EP '653 teaches combining drugs including peptide drugs such as enkephalins with an enhancer of absorption at a mucosal surface and a cyclodextrin. The reference further teaches that undesirable side-effects due to using an absorption enhancer alone may be avoided when an absorption enhancer is used in combination with a cyclodextrin. See Column 3, lines 9-15. The medicaments disclosed by EP '653 are useful for therapy via in intranasal route. In fact, EP '653 teaches that intranasal administration is used as an alternative to oral administration since the included "drugs are only absorbed

poorly by an oral route or are extensively metabolised in the gastrointestinal tract or subjected to first pass metabolism in the liver." See column 1, lines 8-19. Additionally, EP '653 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the drugs used in the disclosed medicaments.

In contrast, the presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy which are preferably administered orally rather than intranasally. EP '653 teaches away from the presently claimed invention by specifically disclosing that the drugs used in the embodied medicaments "are only absorbed poorly by an oral route". The opioid peptides included in the presently claimed inclusion complexes are preferably administered orally, a significant improvement over the teachings of the EP '653 reference. A person of ordinary skill in the art would have had no motivation to combine the references cited by the Examiner to arrive at the presently claimed invention as required by In re Fine in view of the fact that EP '653 teaches away from the presently claimed invention.

Further, applicants claims as presently amended are limited to inclusion complexes containing an opioid peptide and a cyclodextrin derivative as the only essential components. Neither reference

cited by the Examiner teaches inclusion complexes having only these two essential components. As shown above, Nath et al. merely teaches a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, EP '653 teaches inclusion complexes which require a peptide drug, a cyclodextrin derivative, and an enhancer of absorption at a mucosal surface. The absorption enhancer is a critical component of the inclusion complexes taught by EP '653. In contrast, the presently claimed inclusion complexes do not contain an absorption enhancer. Accordingly, the presently claimed invention is patentably distinct from the references cited by the Examiner.

Additionally, as stated above, the presently claimed inclusion complexes provide excellent analgesic effects without any side effects for oral administration. Neither reference cited by the Examiner disclosed inclusion complexes containing an opioid peptide and a cyclodextrin which can be administered orally. Indeed, as evidenced by Uekema et al., *Drug Targeting Delivery*, 1994, 3, 411-456, there is a great deal of uncertainty when it comes to actual formation of complexes with opioid peptides and cyclodextrins. Accordingly, a person of ordinary skill in the art would have had no reasonable expectation of success in forming orally available inclusion complexes containing the specific peptide according to

the presently claimed invention as well as a cyclodextrin as required by Amgen, Inc. v. Chugai Pharm. Co. without an express teaching to do so from the references cited by the Examiner.

In particular, applicants have observed that the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide combined with beta-cyclodextrin in a 1:2 ratio is more effective orally than a 1:1 ratio. In the case of transdermal delivery, the effectiveness of these complexes is reversed. This shows that the formation of the presently claimed inclusion complexes containing this specific opioid peptide and a cyclodextrin would not have been obvious to a person of ordinary skill in the art without an express teaching to do so. Neither reference cited by the Examiner contains such an express teaching. Accordingly, the references cited by the Examiner merely provide an invitation to experiment. These references do not predict that any drug can be combined with cyclodextrins to form orally effective pharmaceutical compositions, nor do they teach how opioid peptides will behave when combined with cyclodextrins.

Additionally, there has been a long felt need for an innovative strategy for oral delivery of peptide based drugs. As shown by Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986), long felt need is a secondary consideration which

may be used as an indicia of non-obviousness. To satisfy this need, applicants have developed pharmaceutical compositions comprising the claimed specific opioid peptide with a cyclodextrin to impart improved analgesic activity with longer duration of action as compared to free peptides (see page 6 of the instant specification). Applicants claimed invention is not a mere combination, but a composition having improved oral efficacy. This is not taught by the cited references, as required by In re Wilson.

Regarding the Examiner's assertion that "the motivation to combine the two references is the desirability of forming a nasally administrable composition comprising the compound of the Nath et al article", applicants respectfully reiterate that this combination is not the same as the presently claimed invention. In particular, the presently claimed invention relates to inclusion complexes which are orally efficacious. See claim 1. The combination suggested by the Examiner is nasally administrable, but is not orally efficacious. Accordingly, the Examiner's proposed combination does not result in the same product as that which is presently claimed.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of EP '653

and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1-3 and 7-11.

3. Rejection of claims 1, 2, 4, 7-12, and 14 are rejected over Hora et al. in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, 4, 7-12, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over Hora et al in view of the Nath et al article. Hora et al teach combining polypeptide drugs with cyclodextrins, B-cyclodextrin, including hydroxyethyl-B-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. . . . Hora et al do not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al. would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-

effective variable which is routinely determined and optimized in the pharmaceutical arts.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. This compound is not the same as the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide used in accordance with the presently claimed invention. The Nath et al. compound is different from the compound used according to the presently pending claims in that it contains a MePhe group, rather than a N-MePhe group. Additionally, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

Hora et al. do not remedy these deficiencies. Hora et al. disclose combining polypeptide drugs with a cyclodextrin to obtain combinations with improved solubility and stability of the polypeptide drugs. Hora et al. provide no teaching that opioid peptides, such as the specific opioid peptide according to the

presently claimed invention, are included among the polypeptide drugs used in the disclosed combinations.

A person of ordinary skill in the art would recognize that the opioid peptide used according to the presently claimed invention is soluble and stable. Accordingly, this peptide does not require improved water solubility or stability. Instead, the presently claimed inclusion complexes provide excellent analgesic effects without any side effects for oral administration. Neither reference cited by the Examiner disclosed inclusion complexes containing an opioid peptide and a cyclodextrin which can be administered orally. Indeed, as evidenced by Uekema et al., *Drug Targeting Delivery*, 1994, 3, 411-456, there is a great deal of uncertainty when it comes to actual formation of complexes with opioid peptides and cyclodextrins. Accordingly, a person of ordinary skill in the art would have had no reasonable expectation of success in forming orally available inclusion complexes containing the specific peptide according to the presently claimed invention as well as a cyclodextrin as required by Amgen, Inc. v. Chugai Pharm. Co. without an express teaching to do so from the references cited by the Examiner.

In particular, applicants have observed that the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide combined

with beta-cyclodextrin in a 1:2 ratio is more effective orally than a 1:1 ratio. In the case of transdermal delivery, the effectiveness of these complexes is reversed. This shows that the formation of the presently claimed inclusion complexes containing this specific opioid peptide and a cyclodextrin would not have been obvious to a person of ordinary skill in the art without an express teaching to do so. Neither reference cited by the Examiner contains such an express teaching. Accordingly, the references cited by the Examiner merely provide an invitation to experiment. These references do not predict that any drug can be combined with cyclodextrins to form orally effective pharmaceutical compositions, nor do they teach how opioid peptides will behave when combined with cyclodextrins.

Accordingly, a person of ordinary skill in the art would have had no motivation to combine these references to arrive at the presently claimed invention without impermissible hindsight. See In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999). The presently claimed complexes were not achieved or suggested by the prior art given that the varying parameters and innumerable possibilities that would have had to be tried until the successful combination was arrived at. Since the prior art does not indicate which parameters are critical, or how the opioid can be expected to

behave with cyclodextrin, the only direction as to which of the many choices is likely to be successful is impermissibly provided by the present application. "When a rejection depends on a combination of prior art references there must be some teaching, suggestion, or motivation to combine these references." In re Rouffet, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). As stated herein, no such motivation is present in the cited references.

Furthermore, one of ordinary skill in the art would not have been motivated to make the claimed invention based on a reference teaching improved solubility where improved solubility is not an object of the invention. The peptide included in the presently claimed invention is already soluble; accordingly, there is no need to improve its solubility or stability as taught by Hora et al. A person of ordinary skill in the art attempting to make orally available inclusion complexes having improved analgesic properties, as required by the presently claimed invention, would have had no motivation to combine the teachings of Nath et al. with the Hora et al. reference related to a completely unrelated art area, i.e. preparation of complexes having improved solubility. Accordingly, the combination cited by the Examiner does not render the presently claimed invention obvious.

Additionally, there has been a long felt need for an innovative strategy for oral delivery of opioid peptide based drugs. As shown by Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986), long felt need is a secondary consideration which may be used as an indicia of non-obviousness. To satisfy this need, applicants have developed pharmaceutical compositions comprising the claimed specific opioid peptide with a cyclodextrin to impart improved analgesic activity with longer duration of action as compared to free opioid peptides (see page 6 of the instant specification). Applicants claimed invention is not a mere combination, but a composition having improved oral efficacy. This is not taught by the cited references, as required by In re Wilson.

Regarding the Examiner's assertion that "Hora et al's description of the cyclodextrins as stabilizing polypeptides in order to maintain their activity...is synonymous with Applicants' desired results of long duration of activity and improved efficacy", this is incorrect. In particular, while the portion of the reference cited by the Examiner does relate to stabilizing polypeptides, it does not disclose that such stabilization is performed in order to maintain the polypeptides activity. In fact, column 19, lines 48-50 implies that most

solubilization/stabilization agents provide an "appreciable loss of activity" to the polypeptides which are being stabilized. Accordingly, Hora et al.'s description of the cyclodextrins as stabilizing polypeptides is not actually synonymous with applicant's claimed inclusion complexes having a prolonged activity.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Hora et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 4, 7-12, and 14.

4. Rejection of claims 1, 7-12, and 15 are rejected over French Patent '268 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 7-12, and 15 are rejected under 35 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with B-cyclodextrin. The combination permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art to at the time Applicants' invention was made to

> administer the opioid peptide of the Nath et al article in the pharmaceutical formulation of French Patent '268 because the opioid peptide of the Nath et al article is a specific known example of the analgesic drugs which are contemplated by the French patent '268, because the French patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al because of the French Patent '268's disclosed ability to administer polypeptide hormones, and because administering the opioid peptide of Nath et al transcutaneously in the pharmaceutical formulations of the French Patent '268 would avoid problems of poor absorption after oral administration or of intrusive i.p. administration methods. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to inclusion complexes comprising an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. This compound is not the same as the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide used in accordance with the presently claimed invention. The Nath et al. compound is different from the compound used according to the presently pending claims in that it contains a MePhe group, rather than a N-MePhe group. Additionally, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

FR '268 does not remedy these deficiencies. FR '268 teaches combining various peptide hormones with a cyclodextrin. This combination permits the drugs to be administered transcutaneously. Indeed, as the Examiner has admitted, FR '268 teaches that transcutaneous administration is used as an alternative to oral administration to "avoid problems of poor absorption after oral administration". Additionally, FR '268 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the drugs used in the disclosed combinations.

In contrast, the presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy which are preferably administered orally rather than transcutaneously. FR '268 teaches away from the presently claimed invention by, as the Examiner has admitted on the record, teaching that that transcutaneous administration is used as an alternative to oral administration to "avoid problems of poor absorption after oral administration". The opioid peptides included in the presently claimed inclusion complexes are preferably administered orally, a significant improvement over the teachings of the FR '268 reference. A person of ordinary skill in the art would have had no motivation to combine the references cited by the Examiner to arrive at the presently claimed invention as required by In re Fine in view of the fact that FR '268 teaches away from the presently claimed invention.

Additionally, as stated above, the presently claimed inclusion complexes provide excellent analgesic effects without any side effects for oral administration. Neither reference cited by the Examiner disclosed inclusion complexes containing an opioid peptide and a cyclodextrin which can be administered orally. Indeed, as evidenced by Uekema et al., *Drug Targeting Delivery*, 1994, 3, 411-456, there is a great deal of uncertainty when it comes to actual

formation of complexes with opioid peptides and cyclodextrins. Accordingly, a person of ordinary skill in the art would have had no reasonable expectation of success in forming orally available inclusion complexes containing the specific peptide according to the presently claimed invention as well as a cyclodextrin as required by Amgen, Inc. v. Chugai Pharm. Co. without an express teaching to do so from the references cited by the Examiner.

In particular, applicants have observed that the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide combined with beta-cyclodextrin in a 1:2 ratio is more effective orally than a 1:1 ratio. In the case of transdermal delivery, the effectiveness of these complexes is reversed. This shows that the formation of the presently claimed inclusion complexes containing this specific opioid peptide and a cyclodextrin would not have been obvious to a person of ordinary skill in the art without an express teaching to do so. Neither reference cited by the Examiner contains such an express teaching. Accordingly, the references cited by the Examiner merely provide an invitation to experiment. These references do not predict that any drug can be combined with cyclodextrins to form orally effective pharmaceutical compositions, nor do they teach how opioid peptides will behave when combined with cyclodextrins.

Additionally, there has been a long felt need for an innovative strategy for oral delivery of peptide based drugs. As shown by Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986), long felt need is a secondary consideration which may be used as an indicia of non-obviousness. To satisfy this need, applicants have developed pharmaceutical compositions comprising the claimed specific opioid peptide with a cyclodextrin to impart improved analgesic activity with longer duration of action as compared to free peptides (see page 6 of the instant specification). Applicants claimed invention is not a mere combination, but a composition having improved oral efficacy. This is not taught by the cited references, as required by In re Wilson.

Regarding the Examiner's assertion that "the motivation used to combine the two references is the desirability of forming a transcutaneously administrable composition comprising the compound of the Nath et al article", applicants respectfully reiterate that this combination is not the same as the presently claimed invention. In particular, the presently claimed invention relates to inclusion complexes which are orally efficacious. See claim 1. The combination suggested by the Examiner is transcutaneously administrable, but is not orally efficacious. Accordingly, the Examiner's proposed combination does not result in the same product as that which is presently claimed.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of FR '268 and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 7-12, and 15.

CONCLUSION

In light of the foregoing, Applicants submit that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of all pending claims 1-12 and 14-15 and allow these claims. Favorable action with an early allowance of the claims is earnestly solicited.

Respectfully submitted,

NATH & ASSOCIATES PLLC

5/3, 2002

Harold L. Novick
Reg. No. 26,011
Customer No. 20529

NATH & ASSOCIATES PLLC
1030 15th Street, N.W.
6th Floor
Washington, D.C. 20005
Tel: (202) 775-8383
Fax: (202) 775-8396

HLN:JLM:JBG:\rfr.82239.wpd

BOX PATENT
Attorney Docket No. 82239

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Group Art Unit: 1653
DWIVEDI et al.	)	Examiner: J. RUSSEL
Serial No. 09/537,088	)	
Filed: March 29, 2000	)	

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix A

Please amend the instant specification as indicated in the following marked up copy of the specification.

Please amend the specification by replacing the paragraph on page 1, lines 2-11 with the following:

--The present invention relates to novel inclusion complexes of a high potent opioid peptide, Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with cyclodextrin derivative. More particularly, the invention relates to Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with cyclodextrin derivatives such as beta-cyclodextrin, hydroxypropyl-beta cyclodextrin, hydroxyethyl-beta-cyclodextrin[.], or Dimethyl-beta cyclodextrin. The invention also relates to a process for the preparation of pharmaceutical compositions containing the inclusion

complexes of opiod peptide and the use thereof in the treatment of alleviating pain and acute inflammation, which can be used as a substitute for narcotic analgesics.--

Please amend the specification by replacing the paragraph on page 1, lines 13-21 with the following:

-- There exists a constant need for preparing novel centrally acting agents which can be utilized as substitute for the narcotic [analgesiscs] analgesics, currently being used, having improved biopharmaceutical properties such as low toxicity, lesser tolerance, longer duration of action and least abuse potential. The development of the peptide as drug is restricted due to its poor oral efficacy. In view of this, it is essential to develop orally active formulations. There has been tremendous emphasis on the development of innovative strategies for the oral delivery of peptide based drugs, with increased water solubility, dissolution, bioavailability and improved oral efficacy.--

Please amend the specification by replacing the paragraph on page 2, lines 11-25 with the following:

--The two best enkephalin analogues that had undergone fairly extensively clinical studies so far, are the Sandoz compound FK-33-824 [Tyr-D-Ala-Gly-Met(o)-01] and the Lilly compound met-keohamid (Tyr-D-Ala-Gly-Phe-MeMet-NH2). [Von Graffenreid, B., del

Pozo, E., Roubicek, J., Krebs, E., Poldinger, W., Burmeister, P. and Kerp, L., Nature, 272, 729 (1978) and Frederickson, R.C.A., Smithwick, E. L., Shuman, R. and Bernis, K.G., Science, 211, 603, (1981) Frederickson, R.C.A., In ['] "Opioid Peptides: Molecular Pharmacology, Bio synthesis and analysis" Rapaka, R.S. and Hawks, R. L. eds. NIDA Research Monograph, *70 367. (1986)*] *FK-33-824* gave only slight preference for μ-receptors and met-kephamid was found essentially non-elective for μ and δ receptors. A strong analgesic effect was exerted by both the compounds by systemic route of administration. However, due to a number of serious side effects produced by FK -33-824 therefore it was no longer pursued for further developments as candidate analgesic drug. Relatively fewer side effects were observed with met-kephamid, but due to its hypotensive effect this compound was also finally abandoned.--

Please amend the specification by replacing the paragraph on page 3 with the following:

-- Another enkephalin analogs Tyr-D-Met-Gly-Phe-Pro-NH_2 [Flodes, J., torok, K., Szekeley, J. I., Borvenderg, J., Karezag, I., Tolna, J., Marosfi, S., Varadi, A., Gara. A., Ronai. A. Z. and Szilaggi, G. Life Sciences 33, Supp. 1, 769 (1983)] and Tyr-Arg-Gly-Phe(*p*-NO_2)-Pro-NH_2 (BW-443C) (SEQ ID NO. 1) [*Follenfani, R.I., Hardy, G.W., Lowe, L.A., Schneider, C. and Smith, T.W. Br. J. Pharmacol. 93, 85,*

(1988) and Kriss, M.G., Gralla, R.J., Clark, R.A., Tyson, L.B. and Groshen, S., J. Clin. Onclol., 6, 663, (1988)] were also shown to be more potent analgesic than morphine but due to number of side effects these compounds were also dropped after initial clinical trials. Similarly, structure activity relationship studies were undertaken in our laboratory and an enkephalin analog Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7 [Raghubir, R., Patnaik, G. K., Sharma, S.D., Mathur, K.B. and Dhawan B.N., In recent progress in chemistry and biology of centrally acting peptides. Dhawan B.N. and Rapaka R.S. eds., 167, (1988) and Indian Patent no. 173568 19.10.1989] synthesized earlier in our laboratory and found to be more potent than morphine following systemic administration. This is a highly μ-receptor selective in central and peripheral assay and produces highly profound and long lasting analgesia. *(C. Nath, G.K. Patnaik, W. Haq, K.B. Mathur, R.C. Srimal, B.N. Dhawan and F. Porreca, Pharmacological Research, 31, 269-273, 1995)* The compound and its process for the synthesis was first disclosed in Indian patent [Indian Patent no. 173568 19.10.1989]. Subsequently chronic and subacute toxicity studies on this compound were carried out and it is now disclosed that this compound is safe and did not produce any noticeable toxic side effects. This compound was also studied for their addiction liabilities and tolerance and found to elicit significantly reduced tolerance and addiction properties as compared to morphine. The compound is virtually devoid of any major CNS

effects like sedation and respiratory depression; it is also virtually devoid of any significant cardiovascular effects. Therefore, this compound has a potential as centrally active analgesic agent, which can be used as a substitute to narcotic analgesics (Morphine and related substances). However, this compound upon oral administration produced poor response and extremely high dose is required to obtain similar magnitude of response as observed after parenteral administration owing to its decomposition and poor absorption. The oral efficacy of the therapeutic agents is considered to be highly desirable, therefore, inspite of a profound analgesia and favourable pharmacological effect and almost devoid of toxic effects, the development of the peptide as drug is restricted due to its poor oral efficacy. In view of this, it is essential to develop orally active formulations.--

Please amend the specification by replacing the paragraph on page 4, lines 1-17 with the following:

--There has been tremendous emphasis[ ] on the development of innovative strategies for the oral delivery of peptide based drugs, *(A Fasano. (1998) TIBTECH., 16, 152-157)* with increased water solubility, dissolution, bioavailability and improved oral efficacy (Z. Shao, 1992). Cyclodextrins are reported in the literature that they increase water solubility, dissolution, bioavailability and stability of compound by forming inclusion

complexes. [R. Krishnamoorthy and A. K. Mitra, Pharma. Res., 9: 1157-1163 (1992)]. Recently it was reported in the literature that the β-cyclodextrin inclusion complex increase the half life of Leu-enkephalin from 45 min to 75 min in case of enzyme hydrolysis with leucine amino peptidase (W. J. Erwin., A. K. Dwivedi, P.A. Holbrook, and M. J. Dey, Pharma Res., 11, 1994, 1698-1703). Therefore, the preparation of inclusion complex of peptides and other substances with cyclodextrin are reported in the literature. The advantage of binding substances into inclusion complexes with cyclodextrin is also known in other substances. US Patent No.4603123, 5840714 and 5855916 disclosed the increased therapeutic efficacy and reduced toxic effects of piroxicam, ibuproxam and acid base type drugs respectively.--

Please amend the specification by inserting on page 5, between lines 14 and 15, the following:

--Brief Description of the Drawings

FIG. 1 shows the preparation of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide.

FIG. 2 shows mass spectrum of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide .

FIG. 3 shows NMK spectrum of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide.

FIG. 4 shows DSC (differential scanning calorimetry)

thermogram of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide.

FIG. 5 shows DSC thermogram in the curve of the obtained product.

FIG. 6 shows NMR spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.

FIG. 7 shows mass spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.

FIG. 8 shows DSC thermogram in the curve of the obtained product.

FIG. 9 shows NMR spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.

FIG. 10 shows DSC thermogram in the curve of the obtained product.

FIG. 11 shows NMR spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with hydroxypropyl-beta-cyclodextrin.--

Please amend the specification by replacing the paragraph on page 6, lines 3-5 with the following:

--In still another embodiment, the inclusion complex comprises L-

Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with [hydroxyehtyl] beta-cyclodextrin.--

Please amend the specification by replacing the paragraph on page 8, line 1 with the following:

--**Methods of preparation**--

Please amend the specification by replacing the paragraph on page 9, lines 1-3 with the following:

--Data on reaction yields, L-Tyrosyl-D-alanyl-glycyl-N-methylphenyl-alanyl-glycyl-isopropylamide content in the complex (determined theoretically and experimentally-spectrophotometric determination at the wavelength of 275 nm) are summarised in Table I.--

Please amend the specification by replacing the paragraph on page 10, line 31 to page 11, line 2 with the following:

--Data on reaction yields, L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide content in the complex (determined theoretically and experimentally- spectrophotometric determination at the wavelength of 275 nm) of the complex formed are summarised in Table 1.--

Please amend the specification by replacing the paragraph

on page 11, line 30 to page 12, line 5 with the following:

--Hydroxyethyl-.beta.-cyclodextrin (1.44 g; 1.0 mmole) was dissolved in water (40 ml). The obtained solution was heated to the temperature of 70.degree. C. and L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide (0.568 g; 1.0 mmole) was added. It was vigorously stirred for another 15 minutes and then the solution was filtered. The filtrate was frozen in liquid nitrogen and lyophilized. Inclusion complex (1.89 g; 94.1 %) of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with hydroxyethyl- .beta.-cyclodextrin was obtained in the form of a white powder in the molar ratio of 1:1. Differential scanning calorimetry and NMR spectrum showed the formation of inclusion complex.--

Please amend the specification by replacing the paragraph on page 13, lines 14-16 with the following:

--Biochemical estimations in blood done at day 30 in rat, and days 0 and 30 in monkeys[)], included glucose, creatinine, urea nitrogen, sodium, potassium SGPT (ALT), alkaline phosphatase (ALP), bilirubin, cholesterol, total serum proteins, albumin and globulin.--

Please amend the specification by replacing the paragraph on page 13, lines 17-21 with the following:

--During necropsy examination of the external surface of the body, all

orifices, and the cranial thoracic and abdominal cavities and their contents was performed. A thorough naked eye examination of size, shape, surface, colour, contours etc of all the important organs and tissues was done. Liver, kidneys, adrenals, brain, heart, lungs, spleen and gonads were weighed, and their relative weights were also calculated.--

Please amend the specification by replacing the paragraph on page 13, line 20 to page 14, line 2 with the following:

--The animals continued to remain active and healthy throughout the period of experimentation. Animals of both drug treated and control groups showed uniform (rats) or irregular (monkeys) trends of gain in body weight. The laboratory investigations showed some minor incidental variations but there was no indication of drug induced damages in the various urinalyses hematological and bloods biochemical values. Also, necropsy (including absolute and relative organ weights of important organs and histopathological examinations) did not reveal any sign of target organ toxicity.--

Please amend the specification by replacing the paragraph on page 14, lines 14-19 with the following:

--The test compounds were administered (subcutaneously or per oral) in graded dose in-groups of 8-10 rats each. Then tail flick latency was determined every 10 minutes till it was near the pre drug

level. Percent of animals exhibiting analgesia was determined at each dose level of various compounds and the ED_{50} along with 95% fiducial limits was calculated [Table 2] by prohibit analysis (Finney, 1971), The duration of analgesic effect was determined at the [peat] peak effect. The analgesia lasted for 5-6 hours after oral administration.--

Please amend the specification by inserting on page 16, between lines 2 and 3, the following:

--**TABLE 4**--

Please amend the specification by replacing the paragraph on page 16, line 28 to page 17, line 6 with the following:

--Polyvinyl alcohol (4 g) and polyvinylpyrrolidone (2 g) were taken in a beaker and stirred at 75°C, 120 ml ethyl alcohol (50% v/v) was slowly added into this to get a fine latex. L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide:beta-cyclodextrin complex (1:1) (1.8) g was taken & suspended in propylene glycol (2 ml) PEG 400 (0.5 ml), poly propylene glycol (2 ml) and [tritan] Triton X-100 (1.5 ml) by using sonicater Polymer latex prepared in earlier step was transferred to it by continuous [sterring] stirring and further stirred for 15 minutes. The hydrogel so formed was uniformly poured into a petri dish and allowed to dry. The next day a yellow coloured patch was obtained. This was covered with the plastic film and cut

into the desired size. The patches so obtained were properly packed in a polythene lined blister type packing to avoid coming into contact with moisture before use.--

#10

Supplemental Amdt B 5/14/02

BOX PATENT

Attorney Docket No. 8223

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Group Art Unit: 1653
DWIVEDI et al.	)	Examiner: J. RUSSEL
Serial No. 09/537,088	)	
Filed: March 29, 2000	)	

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix B

Please amend the instant specification as indicated in the following marked up copy of the specification.

Please amend the specification by replacing the paragraph on page 1, lines 2-11 with the following:

B1

--The present invention relates to novel inclusion complexes of a high potent opioid peptide, Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with cyclodextrin derivative. More particularly, the invention relates to Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with cyclodextrin derivatives such as beta-cyclodextrin, hydroxypropyl-beta cyclodextrin, hydroxyethyl-beta-cyclodextrin, or Dimethyl-beta cyclodextrin. The invention also relates to a process for the preparation of pharmaceutical compositions containing the inclusion

complexes of opiod peptide and the use thereof in the treatment of alleviating pain and acute inflammation, which can be used as a substitute for narcotic analgesics.--

Please amend the specification by replacing the paragraph on page 1, lines 13-21 with the following:

--There exists a constant need for preparing novel centrally acting agents which can be utilized as substitute for the narcotic analgesics, currently being used, having improved biopharmaceutical properties such as low toxicity, lesser tolerance, longer duration of action and least abuse potential. The development of the peptide as drug is restricted due to its poor oral efficacy. In view of this, it is essential to develop orally active formulations. There has been tremendous emphasis on the development of innovative strategies for the oral delivery of peptide based drugs, with increased water solubility, dissolution, bioavailability and improved oral efficacy.--

Please amend the specification by replacing the paragraph on page 2, lines 11-25 with the following:

--The two best enkephalin analogues that had undergone fairly extensively clinical studies so far, are the Sandoz compound FK-33-824 [Tyr-D-Ala-Gly-Met(o)-01] and the Lilly compound met-keohamid (Tyr-D-Ala-Gly-Phe-MeMet-NH2). [Von Graffenreid, B., del

Pozo, E., Roubicek, J., Krebs, E., Poldinger, W., Burmeister, P. and Kerp, L., Nature, 272, 729 (1978) and Frederickson, R.C.A., Smithwick, E. L., Shuman, R. and Bernis, K.G., Science, 211, 603, (1981) Frederickson, R.C.A., In "Opioid Peptides: Molecular Pharmacology, Bio synthesis and analysis" Rapaka, R.S. and Hawks, R. L. eds. NIDA Research Monograph, *70 367. (1986)*] *FK-33-824* gave only slight preference for μ-receptors and met-kephamid was found essentially non-elective for μ and δ receptors. A strong analgesic effect was exerted by both the compounds by systemic route of administration. However, due to a number of serious side effects produced by FK -33-824 therefore it was no longer pursued for further developments as candidate analgesic drug. Relatively fewer side effects were observed with met-kephamid, but due to its hypotensive effect this compound was also finally abandoned.

Please amend the specification by replacing the paragraph on page 3 with the following:

Another enkephalin analogs Tyr-D-Met-Gly-Phe-Pro-NH_2 [Flodes, J., torok, K., Szekeley, J. I., Borvenderg, J., Karezag, I., Tolna, J., Marosfi, S., Varadi, A., Gara. A., Ronai. A. Z. and Szilaggi, G. Life Sciences 33, Supp. 1, 769 (1983)] and Tyr-Arg-Gly-Phe(*p*-NO_2)-Pro-NH_2 (BW-443C) (SEQ ID NO. 1) [*Follenfani, R.I., Hardy, G.W., Lowe, L.A., Schneider, C. and Smith, T.W. Br. J. Pharmacol. 93, 85,*

(1988) and Kriss, M.G., Gralla, R.J., Clark, R.A., Tyson, L.B. and Groshen, S., J. Clin. Onclol., 6, 663, (1988)] were also shown to be more potent analgesic than morphine but due to number of side effects these compounds were also dropped after initial clinical trials. Similarly, structure activity relationship studies were undertaken in our laboratory and an enkephalin analog Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7 [Raghubir, R., Patnaik, G. K., Sharma, S.D., Mathur, K.B. and Dhawan B.N., In recent progress in chemistry and biology of centrally acting peptides. Dhawan B.N. and Rapaka R.S. eds., 167, (1988) and Indian Patent no. 173568 19.10.1989] synthesized earlier in our laboratory and found to be more potent than morphine following systemic administration. This is a highly μ-receptor selective in central and peripheral assay and produces highly profound and long lasting analgesia. *(C. Nath, G.K. Patnaik, W. Haq, K.B. Mathur, R.C. Srimal, B.N. Dhawan and F. Porreca, Pharmacological Research, 31, 269-273, 1995)* The compound and its process for the synthesis was first disclosed in Indian patent [Indian Patent no. 173568 19.10.1989]. Subsequently chronic and subacute toxicity studies on this compound were carried out and it is now disclosed that this compound is safe and did not produce any noticeable toxic side effects. This compound was also studied for their addiction liabilities and tolerance and found to elicit significantly reduced tolerance and addiction properties as compared to morphine. The compound is virtually devoid of any major CNS

effects like sedation and respiratory depression; it is also virtually devoid of any significant cardiovascular effects. Therefore, this compound has a potential as centrally active analgesic agent, which can be used as a substitute to narcotic analgesics (Morphine and related substances). However, this compound upon oral administration produced poor response and extremely high dose is required to obtain similar magnitude of response as observed after parenteral administration owing to its decomposition and poor absorption. The oral efficacy of the therapeutic agents is considered to be highly desirable, therefore, inspite of a profound analgesia and favourable pharmacological effect and almost devoid of toxic effects, the development of the peptide as drug is restricted due to its poor oral efficacy. In view of this, it is essential to develop orally active formulations.--

Please amend the specification by replacing the paragraph on page 4, lines 1-17 with the following:

--There has been tremendous emphasis on the development of innovative strategies for the oral delivery of peptide based drugs, *(A Fasano. (1998) TIBTECH., 16, 152-157)* with increased water solubility, dissolution, bioavailability and improved oral efficacy (Z. Shao, 1992). Cyclodextrins are reported in the literature that they increase water solubility, dissolution, bioavailability and stability of compound by forming inclusion

complexes. [R. Krishnamoorthy and A. K. Mitra, Pharma. Res., 9: 1157-1163 (1992)]. Recently it was reported in the literature that the β-cyclodextrin inclusion complex increase the half life of Leu-enkephalin from 45 min to 75 min in case of enzyme hydrolysis with leucine amino peptidase (W. J. Erwin., A. K. Dwivedi, P.A. Holbrook, and M. J. Dey, Pharma Res., 11, 1994, 1698-1703). Therefore, the preparation of inclusion complex of peptides and other substances with cyclodextrin are reported in the literature. The advantage of binding substances into inclusion complexes with cyclodextrin is also known in other substances. US Patent No.4603123, 5840714 and 5855916 disclosed the increased therapeutic efficacy and reduced toxic effects of piroxicam, ibuproxam and acid base type drugs respectively.--

Please amend the specification by inserting on page 5, between lines 14 and 15, the following:

--**Brief Description of the Drawings**

FIG. 1 shows the preparation of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide.

FIG. 2 shows mass spectrum of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide .

FIG. 3 shows NMK spectrum of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide.

FIG. 4 shows DSC (differential scanning calorimetry)

thermogram of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide.

FIG. 5 shows DSC thermogram in the curve of the obtained product.

FIG. 6 shows NMR spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.

B6 Conclude

FIG. 7 shows mass spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.

FIG. 8 shows DSC thermogram in the curve of the obtained product.

FIG. 9 shows NMR spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.

FIG. 10 shows DSC thermogram in the curve of the obtained product.

FIG. 11 shows NMR spectrum of the complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with hydroxypropyl-beta-cyclodextrin.--

Please amend the specification by replacing the paragraph on page 6, lines 3-5 with the following:

--In still another embodiment, the inclusion complex comprises L-

B7

B7 conclude

Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with beta-cyclodextrin.--

Please amend the specification by replacing the paragraph on page 8, line 1 with the following:

--**Methods of preparation**--

B8

Please amend the specification by replacing the paragraph on page 9, lines 1-3 with the following:

--Data on reaction yields, L-Tyrosyl-D-alanyl-glycyl-N-methylphenyl-alanyl-glycyl-isopropylamide content in the complex (determined theoretically and experimentally-spectrophotometric determination at the wavelength of 275 nm) are summarised in Table I.--

B9

Please amend the specification by replacing the paragraph on page 10, line 31 to page 11, line 2 with the following:

--Data on reaction yields, L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide content in the complex (determined theoretically and experimentally- spectrophotometric determination at the wavelength of 275 nm) of the complex formed are summarised in Table 1.--

B10

Please amend the specification by replacing the paragraph

on page 11, line 30 to page 12, line 5 with the following:

--Hydroxyethyl-.beta.-cyclodextrin (1.44 g; 1.0 mmole) was dissolved in water (40 ml). The obtained solution was heated to the temperature of 70.degree. C. and L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide (0.568 g; 1.0 mmole) was added. It was vigorously stirred for another 15 minutes and then the solution was filtered. The filtrate was frozen in liquid nitrogen and lyophilized. Inclusion complex (1.89 g; 94.1 %) of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with hydroxyethyl- .beta.-cyclodextrin was obtained in the form of a white powder in the molar ratio of 1:1. Differential scanning calorimetry and NMR spectrum showed the formation of inclusion complex.--

B11

Please amend the specification by replacing the paragraph on page 13, lines 14-16 with the following:

--Biochemical estimations in blood done at day 30 in rat, and days 0 and 30 in monkeys, included glucose, creatinine, urea nitrogen, sodium, potassium SGPT (ALT), alkaline phosphatase (ALP), bilirubin, cholesterol, total serum proteins, albumin and globulin.--

B12

Please amend the specification by replacing the paragraph on page 13, lines 17-21 with the following:

--During necropsy examination of the external surface of the body, all

B13

orifices, and the cranial thoracic and abdominal cavities and their contents was performed. A thorough naked eye examination of size, shape, surface, colour, contours etc of all the important organs and tissues was done. Liver, kidneys, adrenals, brain, heart, lungs, spleen and gonads were weighed, and their relative weights were also calculated.--

B13 conclude

Please amend the specification by replacing the paragraph on page 13, line 20 to page 14, line 2 with the following:

--The animals continued to remain active and healthy throughout the period of experimentation. Animals of both drug treated and control groups showed uniform (rats) or irregular (monkeys) trends of gain in body weight. The laboratory investigations showed some minor incidental variations but there was no indication of drug induced damages in the various urinalyses hematological and bloods biochemical values. Also, necropsy (including absolute and relative organ weights of important organs and histopathological examinations) did not reveal any sign of target organ toxicity.--

B14

Please amend the specification by replacing the paragraph on page 14, lines 14-19 with the following:

--The test compounds were administered (subcutaneously or per oral) in graded dose in-groups of 8-10 rats each. Then tail flick latency was determined every 10 minutes till it was near the pre drug

B15

level. Percent of animals exhibiting analgesia was determined at each dose level of various compounds and the ED_{50} along with 95% fiducial limits was calculated [Table 2] by prohibit analysis (Finney, 1971), The duration of analgesic effect was determined at the peak effect. The analgesia lasted for 5-6 hours after oral administration.

Please amend the specification by inserting on page 16, between lines 2 and 3, the following:

--TABLE 4

Please amend the specification by replacing the paragraph on page 16, line 28 to page 17, line 6 with the following:

--Polyvinyl alcohol (4 g) and polyvinylpyrrolidone (2 g) were taken in a beaker and stirred at 75°C, 120 ml ethyl alcohol (50% v/v) was slowly added into this to get a fine latex. L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide:beta-cyclodextrin complex (1:1) (1.8) g was taken & suspended in propylene glycol (2 ml) PEG 400 (0.5 ml), poly propylene glycol (2 ml) and Triton X-100 (1.5 ml) by using sonicater Polymer latex prepared in earlier step was transferred to it by continuous stirring and further stirred for 15 minutes. The hydrogel so formed was uniformly poured into a petri dish and allowed to dry. The next day a yellow coloured patch was obtained. This was covered with the plastic film and cut into the

desired size. The patches so obtained were properly packed in a polythene lined blister type packing to avoid coming into contact with moisture before use.

BOX PATENT
Attorney Docket No. 82239

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:) Group Art Unit: 1653

DWIVEDI et al.) Examiner: J. RUSSEL

Serial No. 09/537,088)

Filed: March 29, 2000)

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix C

Please amend claims 1 and 8 as indicated in the following marked up copy of the claims.

1. (Twice Amended) An orally efficacious and prolonged duration of action inclusion complex, [comprising] consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative.

8. (Twice Amended) Pharmaceutical compositions [comprising] consisting essentially of a therapeutically effective amount of inclusion complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with the cyclodextrin derivative as claimed in claim 1 having improved analgesic

activity with longer duration of action as compared with the free peptide.

#10

BOX PATENT

Attorney Docket No. 32239

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Group Art Unit: 1653
DWIVEDI et al.	)	Examiner: J. RUSSEL
Serial No. 09/537,088	)	
Filed: March 29, 2000	)	

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix D

Please amend claims 1 and 8 as indicated in the following clean copy of the claims.

B18

1. (Twice Amended) An orally efficacious and prolonged duration of action inclusion complex, consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative.

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8. (Twice Amended) Pharmaceutical compositions consisting essentially of a therapeutically effective amount of inclusion complex of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with the cyclodextrin derivative as claimed in claim 1 having improved analgesic activity with

Bridge
Orchestrate longer duration of action as compared with the free peptide.